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(54) **Citalopram hydrobromide crystal and method for crystallization thereof**

(57) According to the present invention, citalopram hydrobromide dissolved in a solvent containing at least one member selected from the group consisting of alcohol having 1 - 3 carbon atoms, water and acetone is crystallized or recrystallized while controlling the cooling rate, thereby to 1) provide an industrial method for crys-

tallizing citalopram hydrobromide, which enables easy control of the crystal characteristics, such as particle size, particle size distribution and aspect ratio and the like of the crystal, and 2) provide citalopram hydrobromide crystal having crystal characteristics useful as a pharmaceutical bulk.

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Description

TECHNICAL FIELD OF THE INVENTION

5 [0001] The present invention relates to a method for crystallizing citalopram hydrobromide useful as an antidepressant and citalopram hydrobromide having specific crystal properties.

BACKGROUND OF THE INVENTION

10 [0002] Citalopram hydrobromide is useful as an antidepressant. When it is used as a pharmaceutical bulk for the preparation of a pharmaceutical agent, particle size, particle size distribution and aspect ratio of the crystal are the important crystal characteristics. However, there is no teaching as to what crystal characteristics of citalopram hydrobromide are required as a beneficial pharmaceutical bulk, or a method for achieving such beneficial crystal characteristics.

15 [0003] According to US4650884, for example, a method for crystallizing citalopram hydrobromide comprises, crystallization in a single solvent of acetone, first recrystallization in a single solvent of water, second recrystallization in a mixed solvent of methanol and isopropyl alcohol, and third recrystallization in a mixed solvent of methanol, acetone and hexane. This method aims at purification of citalopram crystals but not at controlling particle size, particle size distribution or aspect ratio of crystals, not to mention a method for controlling these.

20 [0004] When citalopram hydrobromide is crystallized according to the method described in this publication, fine crystals having a particle size of less than 5 μm are formed in a large amount (41.9% of the total amount). When fine crystals are contained in a large amount, filtering performance after crystallization for medicament production is degraded. In addition, the fine particles scatter and the workers are exposed thereto during production of pharmaceutical preparations, which is an unpreferable aspect as a pharmaceutical bulk.

25 [0005] When citalopram hydrobromide is crystallized according to the method described in this publication, crystals having a smaller average aspect ratio of less than 2 are produced. Such crystals cause problems such as poor filtering performance after crystallization for the preparation of a pharmaceutical agent and poor fluidity when crystals are being taken out, which is not preferable as a pharmaceutical bulk.

30 [0006] It is therefore an object of the present invention to provide

- (1) a method for industrially crystallizing citalopram hydrobromide, which method affords easy control of crystal characteristics, such as particle size, particle size distribution and aspect ratio of the crystals, and
- (2) citalopram hydrobromide crystals having crystal characteristics useful as a pharmaceutical bulk.

35 SUMMARY OF THE INVENTION

[0007] Such object can be achieved by the present invention. According to the present invention, citalopram hydrobromide dissolved in a specific solvent is crystallized or recrystallized while controlling the cooling rate, thereby to control the particle size, particle size distribution and aspect ratio of citalopram hydrobromide crystals. It has been also found that citalopram hydrobromide crystals containing crystals having a particle size of less than 5 μm in a proportion of 35% at most and citalopram hydrobromide crystals having an average aspect ratio of not less than 4.5 and not more than 6.0, which are obtained by this method, are advantageous as a pharmaceutical bulk.

40 [0008] Accordingly, the present invention provides the following.

- 45 (1) Citalopram hydrobromide crystals containing crystals having a particle size of less than 5 μm in a proportion of 35% at most.
- (2) Citalopram hydrobromide crystals containing crystals having a particle size of less than 5 μm in a proportion of 35% at most, and containing crystals having a particle size of not less than 20 μm in a proportion of not less than 10%, or having an average aspect ratio of not less than 2.0 and not more than 9.0, or having an average aspect ratio of not less than 2.5 and less than 4.5, or having an average aspect ratio of not less than 4.5 and not more than 6.0.
- 50 (3) Citalopram hydrobromide crystals having an average aspect ratio of not less than 2.0 and not more than 9.0.
- (4) Citalopram hydrobromide crystals having an average aspect ratio of not less than 2.5 and less than 4.5.
- (5) Citalopram hydrobromide crystals having an average aspect ratio of not less than 4.5 and not more than 6.0.
- 55 (6) A method for crystallizing citalopram hydrobromide, which comprises the steps of

(A1) dissolving, by heating, citalopram hydrobromide in a solvent containing at least one member selected from the group consisting of alcohol having 1 to 3 carbon atoms, water and acetone and

(B1) cooling the resulting product to achieve crystallization, while controlling the cooling rate.

(7) A method for crystallizing citalopram hydrobromide, which comprises the steps of

- (A2) dissolving, by heating, citalopram hydrobromide in a solvent containing at least one member selected from the group consisting of alcohol having 1 to 3 carbon atoms, water and acetone,
- (B2) cooling the obtained solution to achieve crystallization,
- (C2) dissolving a part of the obtained crystals by heating, and
- (D2) recrystallizing the crystals while controlling the cooling rate.

[0009] A preferable mode of the above-mentioned (6) includes

- (6-1) controlling the cooling rate within the temperature range of 0°C - 80°C,
- (6-2) controlling the average cooling rate within the temperature range of 20°C - 40°C to not less than 30°C/hour and not more than 60°C/hour,
- (6-3) controlling the average cooling rate within the temperature range of 20°C - 40°C to not less than 0.5°C/hour and less than 30°C/hour, and
- (6-4) cooling the solution obtained in (A1) to a temperature range of not less than 30°C and less than 48°C and adding a seed crystal of citalopram hydrobromide to achieve crystallization.

[0010] A preferable mode of the above-mentioned (7) includes

- (7-1) cooling to the temperature range of not less than 30°C and less than 48°C in (B2),
- (7-2) after cooling to the temperature range of not less than 30°C and less than 48°C, adding a seed crystal of citalopram hydrobromide to achieve crystallization in (B2),
- (7-3) heating to the temperature range of not less than 48°C and not more than 60°C to dissolve a part of the crystal in (C2),
- (7-4) controlling the average cooling rate in the temperature range of from (heating temperature in (C2)) to (this heating temperature - 30°C) to not less than 30°C/hour and not more than 90°C/hour in (D2), and
- (7-5) controlling the average cooling rate in the temperature range of from (heating temperature in (C2)) to (this heating temperature - 30°C) to not less than 1°C/hour and less than 30°C/hour in (D2).

BRIEF DESCRIPTION OF THE DRAWINGS

[0011]

- Figure 1 shows ¹H-NMR of the compound obtained in Reference Example 1.
- Figure 2 shows a powder X-ray crystal diffraction pattern of the compound obtained in Reference Example 1.
- Figure 3 shows a powder X-ray crystal diffraction pattern of the compound obtained in Example 1.
- Figure 4 shows a powder X-ray crystal diffraction pattern of the compound obtained in Example 4.
- Figure 5 shows a powder X-ray crystal diffraction pattern of the compound obtained in Comparative Example 1.
- Figure 6 shows a crystal particle size distribution of the compound obtained in Example 1.
- Figure 7 shows a crystal particle size distribution of the compound obtained in Example 2.
- Figure 8 shows a crystal particle size distribution of the compound obtained in Example 3.
- Figure 9 shows a crystal particle size distribution of the compound obtained in Example 4.
- Figure 10 shows a crystal particle size distribution of the compound obtained in Example 5.
- Figure 11 shows a crystal particle size distribution of the compound obtained in Example 6.
- Figure 12 shows a crystal particle size distribution of the compound obtained in Comparative Example 1.
- Figure 13 shows a micrograph (400 magnifications) of the compound obtained in Example 1.
- Figure 14 shows a micrograph (400 magnifications) of the compound obtained in Example 4.
- Figure 15 shows a micrograph (400 magnifications) of the compound obtained in Example 6.
- Figure 16 shows a micrograph (400 magnifications) of the compound obtained in Comparative Example 1.
- Figure 17 shows a micrograph (400 magnifications) of a ruler graduated in 10 μm.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The present invention is explained in detail in the following.

[0013] The average particle size in the present invention is an average diameter upon conversion of the volume of

the crystal particles into sphere.

[0014] The average aspect ratio in the present invention is an average value of the major axis/minor axis of crystal particles.

5 [0015] According to the present invention, crystal characteristics such as particle size, particle size distribution and aspect ratio of the crystals can be controlled easily. As the industrial method for crystallizing citalopram hydrobromide includes the following methods.

Method 1

10 [0016] A first method for crystallizing citalopram hydrobromide in the present invention includes

(A1) dissolving citalopram hydrobromide in a specific solvent, and

(B1) crystallization by cooling the resulting solution while controlling a cooling rate

15 (hereinafter this method is to be referred to as Method 1). The crystals obtained according to Method 1 generally show a smooth cone-shaped particle size distribution.

[0017] In the following, the steps (A1) and (B1) are explained in detail. In each step, it is preferable that the particles be stirred at 10 rpm - 250 rpm, particularly at 50 rpm - 220 rpm, so that the temperature of the system as a whole can be uniform and the crystals after stirring will not have a smaller aspect ratio.

20 [0018] According to Method 1, the cooling rate of the solution within the specific temperature range should be regulated to control the crystal characteristics. That is, the present inventors have found that the cooling rate of the solution within the temperature range of preferably 0°C - 80°C, particularly 20°C-40°C, in (B1) affects the crystal particle size of citalopram hydrobromide. For example, the crystals obtained when the average cooling rate of the solution within the temperature range of 20°C - 40°C is controlled to not less than 0.5°C/hour and less than 30°C/hour contain crystals
25 having a particle size of less than 5 µm in a proportion of 35% at most, and have an average particle size of about 10 µm - 20 µm, and that the crystals obtained when it is controlled to not less than 30°C/hour and not more than 60°C/hour contain crystals having a particle size of less than 5 µm in a proportion of 35% at most, and have an average particle size of about 7 µm - 15 µm. Cooling within the above-mentioned temperature range is preferably conducted such that the cooling rate becomes almost constant.

30 [0019] A next important process for controlling the crystal characteristics is the addition of seed crystal in (B1) in the specific temperature range. Addition of a seed crystal for crystallization of a compound is a known preferable method for precipitating crystals, as demonstrated in US4650884 with regard to citalopram hydrobromide. In this publication, a seed crystal is added when the cooling temperature is 20°C. By reproductive crystallization according to this method by the present inventors, it was revealed that suitable growth of the precipitated crystals was not achieved, with a
35 considerable amount of fine crystals having a particle size of less than 5 µm. When fine crystals are contained in a great amount, filterability after crystallization for the preparation of a pharmaceutical bulk becomes poor, and the fine particles scatter, to which particles the workers are exposed during production of pharmaceutical preparations.

[0020] The present inventors have also found that, in (B1), cooling to the temperature range of preferably not less than 30°C and less than 48°C, more preferably not less than 40°C and less than 48°C, followed by addition of a seed
40 crystal to allow for crystallization, results in precipitation of crystals suitably grown. Thus, the particle size of the crystals can be controlled well, and generation of fine crystals having a particle size of less than 5 µm can be further inhibited by this method.

[0021] When the temperature, at which a seed crystal is added, is less than 30°C, crystallization occurs at once and fine crystals tend to increase. When it is not less than 48°C, the seed crystal tends to dissolve easily, and the effect of
45 the addition of the seed crystal becomes low. The amount of the seed crystal added is not subject to any particular limitation, but it is preferably 0.0001 wt% - 1 wt%, more preferably 0.001 wt% - 0.01 wt%, relative to citalopram hydrobromide used for crystallization.

[0022] In (A1) in Method 1, citalopram hydrobromide is dissolved in a specific solvent preferably by heating to 50°C - 80°C, more preferably 55°C - 75°C.

50 [0023] The specific solvent used in Method 1 contains at least one member selected from the group consisting of alcohol having 1 to 3 carbon atoms (e.g., methanol, ethanol, isopropyl alcohol, 1-propanol), water and acetone, in a proportion of preferably not less than 70 wt%, more preferably not less than 80 wt%. The solvent that may be contained in addition to alcohol having 1 to 3 carbon atoms, water and acetone is not subject to any particular limitation, and may be any as long as it is miscible with these solvents and is not reactive with citalopram hydrobromide. Examples thereof
55 include toluene, xylene, tetrahydrofuran, diisopropyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether and the like. These may be used alone or in a combination of 2 or more solvents, wherein the boiling point thereof is preferably higher than the above-mentioned heating temperature. More preferable examples of the above-mentioned specific solvent include those containing at least one member selected from the group consisting of methanol, ethanol,

isopropyl alcohol and 1-propanol in a proportion of not less than 80 wt%, particularly preferably those containing methanol and isopropyl alcohol in a proportion of not less than 90 wt%.

[0024] The amount of the above-mentioned specific solvent varies depending on the kind of each solvent used solely or in combination, the temperature at which citalopram hydrobromide is heated for dissolution and the like. However, it is generally preferably 2 L - 30 L, more preferably 4 L - 16 L, per 1 kg of citalopram hydrobromide. When a mixed solvent containing methanol and isopropyl alcohol is used, it is particularly preferable that the amounts thereof be 2 L - 5 L of methanol and 4 L - 8 L of isopropyl alcohol, both per 1 kg of citalopram hydrobromide.

[0025] According to Method 1, after the completion of step 2, the crystallization of citalopram hydrobromide is preferably completed after aging at a temperature below the final cooling temperature (preferably -10°C to 30°C, more preferably 0°C to 20°C) for preferably 30 minutes - 48 hours, more preferably 2 hours - 24 hours, to achieve an improved yield.

[0026] By the foregoing steps, the characteristics of citalopram hydrobromide crystals can be controlled. For example, to shift the particle size distribution of the crystals toward that of the crystals having a greater particle size, the cooling rate may be slowed or a seed crystal may be added in (B1). To increase the aspect ratio, the cooling rate or the stirring speed may be slowed in (B1).

Method 2

[0027] The second method for crystallizing citalopram hydrobromide according to the present invention includes the steps of:

- (A2) dissolving citalopram hydrobromide in a specific solvent by heating,
- (B2) crystallizing citalopram hydrobromide by cooling the obtained solution,
- (C2) heating the resulting crystals to dissolve a part of the obtained crystals, and
- (D2) recrystallizing citalopram hydrobromide while controlling a cooling rate

(hereinafter this method is to be referred to as Method 2). The crystals obtained in Method 2 generally contain fine crystals in a smaller proportion than in Method 1. In Method 2, the steps of (A2) to (D2) can be performed in one pot. In each step, it is preferable that the particles be stirred at 10 rpm - 250 rpm, particularly at 50 rpm - 220 rpm, so that the temperature of the system as a whole will be uniform and the crystals after stirring will not have a smaller aspect ratio.

[0028] In Method 2, the control of the cooling rate of the solution within the specific temperature range in (D2) is particularly important for the control of the crystal characteristics. That is, the present inventors have found that the cooling rate of the solution particularly within the temperature range of from (heating temperature in (C2)) to (this heating temperature - 30°C) in (D2) in Method 2 affects the crystal particle size of the ultimate crystals. For example, the crystals obtained when the average cooling rate of the solution within this temperature range is controlled to not less than 30°C/hour and not more than 90°C/hour contain crystals having a particle size of less than 5 µm in a proportion of 35% at most, particularly not more than 25%, and have an average particle size of about 10 µm - 25 µm. The crystals obtained when it is controlled to not less than 1°C/hour and less than 30°C/hour contain crystals having a particle size of less than 5 µm in a proportion of 35% at most, particularly not more than 15%, and have an average particle size of about 15 µm - 30 µm. Cooling within the above-mentioned temperature range is preferably conducted such that the cooling rate becomes almost constant.

[0029] A next important process for controlling the crystal characteristics is the addition of a seed crystal within the specific temperature range in (B2) and dissolution by heating in (C2).

[0030] In (B2), the solution obtained in (A2) is cooled to the temperature range of preferably not less than 30°C and less than 48°C, particularly preferably not less than 40°C and less than 48°C. The present inventors have found that, in (B2), cooling to the temperature range of preferably not less than 30°C and less than 48°C, particularly preferably not less than 40°C and less than 48°C, which is followed by addition of a seed crystal to allow for crystallization results in the precipitation of crystals suitably grown. Thus, the particle size of the crystals can be controlled well, and generation of fine crystals having a particle size of less than 5 µm can be further inhibited.

[0031] When the temperature at which a seed crystal is added is less than 30°C, crystallization occurs at once and fine crystals tend to increase. When it is not less than 48°C, the seed crystal tends to dissolve easily, and the effect of the addition of the seed crystal becomes low. The amount of the seed crystal added is not subject to any particular limitation, but it is preferably 0.0001 wt% - 1 wt%, more preferably 0.001 wt% - 0.01 wt%, relative to citalopram hydrobromide used for crystallization.

[0032] In (C2), a part of the crystals obtained in (B2) is dissolved by heating, thereby preventing complete dissolution of the obtained crystals. This has a consequence that the finally obtained crystals have a greater average particle size. This is considered to be attributable to the fact that the crystals not dissolved by heating in (B2) become the seed

crystal in (D2). Therefore, combined with the addition of the seed crystal in (B2), crystals having a greater average particle size as compared to that obtained without such combination can be ultimately obtained. As used herein, the "part of the crystals obtained in (B2)" is not subject to any particular limitation, but it is preferably 10 wt% - 90 wt%, more preferably 20 wt% - 80 wt%, of the crystals obtained in (B2).

5 [0033] The temperature in (C2) is not subject to any particular limitation as long as it can dissolve only a part of the crystals obtained in (B2). Note that the crystals should not be dissolved completely in (B2). It is preferable that a part of the crystals be dissolved by heating to not less than 48°C and not more than 60°C, particularly not less than 48°C and not more than 55°C. When this temperature is less than 48°C, the crystals cannot be dissolved to the desired degree in this step, and when it exceeds 60°C, the crystals are dissolved to the degree beyond the intended degree
10 in this step, both causing an increase in the content of the crystals having a particle size of less than 5 µm, as compared to (C2) performed in the above-mentioned temperature range.

[0034] In Method 2, the cooling rate controlled in (B2) also affects the particle size of the final crystals, as is the case with the aforementioned control of cooling rate in (D2), only to a smaller degree than in (D2). In (B2), the present inventors have found that the cooling rate within the temperature range of preferably 0°C - 80°C, particularly 20°C -
15 40°C, affects the crystal particle size of citalopram hydrobromide. The cooling in the above-mentioned temperature range is preferably performed such that the cooling rate becomes almost the same.

[0035] In (A2) in Method 2, citalopram hydrobromide is dissolved in a specific solvent preferably by heating to 50°C - 80°C, more preferably 55°C - 75°C.

[0036] The specific solvent used in Method 2 contains at least one member selected from the group consisting of alcohol having 1 to 3 carbon atoms (e.g., methanol, ethanol, isopropyl alcohol, 1-propanol), water and acetone, preferably in a proportion of not less than 70 wt%, more preferably not less than 80 wt%. The solvent that may be contained in addition to alcohol having 1 to 3 carbon atoms, water and acetone is not subject to any particular limitation, and may be any as long as it is miscible with these solvents and is not reactive with citalopram hydrobromide. Examples thereof include toluene, xylene, tetrahydrofuran, diisopropyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether and
20 the like. These may be used alone or in a combination of 2 or more solvents, wherein the boiling point thereof is preferably higher than the above-mentioned heating temperature. More preferable examples of the above-mentioned specific solvent include those containing at least one member selected from the group consisting of methanol, ethanol, isopropyl alcohol and 1-propanol in a proportion of not less than 80 wt%. Those containing methanol and isopropyl alcohol in a proportion of not less than 90 wt% are particularly preferable.

30 [0037] The amount of the above-mentioned specific solvent varies depending on the kind of each solvent used solely or in combination, the temperature at which citalopram hydrobromide is heated for dissolution and the like. However, it is generally preferably 2 L - 30 L, more preferably 4 L - 16 L, per 1 kg of citalopram hydrobromide. When a mixed solvent containing methanol and isopropyl alcohol is used, it is particularly preferable that the amounts thereof be 2 L - 5 L of methanol and 4 L - 8 L of isopropyl alcohol, both per 1 kg of citalopram hydrobromide.

35 [0038] In Method 2, (C2) and (D2) may be sequentially repeated after (D2). The crystallization of citalopram hydrobromide is preferably completed after aging at a temperature below the final cooling temperature (preferably -10°C to 30°C, more preferably 0°C to 20°C) for preferably 30 minutes - 48 hours, more preferably 2 hours - 24 hours, to achieve an improved yield.

40 [0039] By the foregoing steps, the characteristics of citalopram hydrobromide crystals can be controlled. For example, to shift the particle size distribution of the crystals toward that of the crystals having a greater particle size, the cooling rate may be slowed in (B2) and (D2), a seed crystal may be added in (B2), and the crystals may be heated for dissolution at a specific temperature in (C2). To increase the aspect ratio, the cooling rate or the stirring speed may be slowed in (B2) and (D2).

45 [0040] In Method 1 and Method 2, the obtained crystals are isolated and purified by conventional methods, such as washing with a suitable solvent after filtration.

[0041] The citalopram hydrobromide crystals wherein 35% at most, preferably not more than 30%, more preferably not more than 20%, thereof has a crystal particle size of less than 5 µm, and further the crystals wherein not less than 10%, more preferably not less than 20%, thereof preferably has a particle size of not less than 20 µm, can improve the filterability after crystallization for the production of pharmaceutical bulk and the like. In addition, they can improve
50 the problems of scattering of fine particles and exposure of the workers to the fine particles during production of a pharmaceutical preparation, and the like. These crystals can be obtained by each method as follows.

[0042] In Method 1, the average cooling rate of the solution within the temperature range of from 20°C to 40°C in (B1) is controlled to not less than 0.5°C/hour and not more than 60°C/hour, preferably by adding a seed crystal at a temperature range of not less than 30°C and less than 48°C in (B1).

55 [0043] In Method 2, the cooling rate of the solution in the temperature range of from ((heating temperature in (C2)) to (this heating temperature - 30°C)) in (D2) is controlled to not less than 1°C/hour and not more than 90°C/hour, or preferably a seed crystal is added at a temperature range of not less than 30°C and less than 48°C in (B2), or a part of the obtained crystals in (B2) is heated for dissolution in (C2).

[0044] The citalopram hydrobromide crystals having an average aspect ratio of generally not less than 2.0, preferably not less than 3, and more preferably not less than 4.5, and generally not more than 9.0, preferably not more than 7, and more preferably not more than 6.0, can improve the problems such as poor filtering performance after crystallization for the preparation of a pharmaceutical bulk and poor fluidity when crystals are being taken out, and can be advantageously used for the production of citalopram hydrobromide and the production of pharmaceutical products. From this viewpoint, the crystals having an average aspect ratio of not less than 4.5 and not more than 6.0 are particularly preferable. These crystals can be obtained by each method as follows.

[0045] In Method 1, the average cooling rate of the solution in the temperature range of 20°C - 40°C in (B1) is controlled to not less than 0.5°C/hour and not more than 60°C/hour, and preferably the stirring speed is set for 10 rpm - 250 rpm in (B1). In (B1), the speed at the tip of an agitation part is generally set to 0.1 m/s - 2.5 m/s, preferably 0.5 m/s - 2.0 m/s.

[0046] In Method 2, the cooling rate of the solution within the temperature range of from (heating temperature in (C2)) to (this heating temperature - 30°C) is controlled to not less than 1°C/hour and not more than 90°C/hour in (D2), and preferably the stirring speed is set for 10 rpm - 250 rpm in (B2) and (D2). In (B2) and (D2), the speed at the tip of an agitation part is generally set to 0.1 m/s - 2.5 m/s, preferably 0.5 m/s - 2.0 m/s.

[0047] By setting the speed at the tip of an agitation part to generally from not less than 2.5 m/s to less than 5.0 m/s, preferably from not less than 3.0 m/s to not more than 4.0 m/s, in (B1) in Method 1 and (B2) and (D2) in Method 2, crystals having an average aspect ratio of not less than 2.5 and less than 4.5 can be obtained. The crystals having an average aspect ratio of not less than 2.5 and less than 4.5 are preferable because they can be used as they are as a pharmaceutical preparation.

[0048] The citalopram hydrobromide to be used may be any that can be obtained by any method. It is preferably purified by active charcoal and the like before being subjected to the crystallization according to the present invention. The citalopram hydrobromide can be obtained, for example, according to the disclosure in, for example, US4650884.

[0049] The present invention is explained in more detail in the following by referring to Examples that do not limit the present invention in any way.

[0050] The powder X-ray crystal diffraction and average particle size were measured in the following Reference Example, Examples and Comparative Example, according to the following methods.

Powder X-ray crystal diffraction: Rigaku Corporation
MiniFlex
Irradiated X-ray CuK α

Average particle size: SHIMADZU CORPORATION SALD1100
(medium : diisopropyl ether)

Reference Example 1

[0051] Citalopram base (167 g) was dissolved in acetone (837 ml). Thereto was blown in a hydrobromic acid gas at 15°C - 40°C to make the pH of the solution 3. When about 1/2 of the hydrobromic acid gas was blown in, crystals began to precipitate. The reaction mixture was stirred at 25°C - 35°C for 1 hour, and at 0°C - 5°C for 1 hour. The resulting crystals were filtered, washed with cold acetone (167 ml) and dried in vacuo at 50°C - 70°C (5 Torr - 30 Torr) for 3 hours to give citalopram hydrobromide crystals (162 g). The crystals had an HPLC purity of 97.3% (254 nm).

melting point 180.3°C

¹H-NMR (DMSO-d₆, 400 MHz): shown in Figure 1.

Powder X-ray crystal diffraction pattern: shown in Figure 2.

Example 1

[0052] Citalopram hydrobromide (5.0 g) was synthesized according to Reference Example 1 and dissolved in methanol (15 ml) at 60°C. Thereto was added active charcoal (0.5 g) and the mixture was stirred for 15 minutes. The active charcoal was filtered off and isopropyl alcohol (25 ml) was added. The mixture was heated to 58°C to dissolve the crystals. When the mixture was cooled to 43°C while stirring at 200 rpm (propeller diameter: 0.05 m, speed at the tip of propeller: $0.05 \times (200/6) \times 3.14 = \text{ca. } 0.5 \text{ m/s}$), the seed crystal (about 0.1 mg) of citalopram hydrobromide was added. The mixture was cooled to 40°C over 15 minutes and then cooled from 40°C to 20°C over 5 hours while stirring at 200 rpm to make the cooling rate almost the same (average cooling rate: 4°C/hour). The cooled suspension was stirred at 20°C for 18 hours (retention time at 20°C) at 200 rpm and the resulting crystals were filtrated. The crystals were dried at 50°C (0.67 kPa - 1.33 kPa) for 3 hours in vacuo while stirring them at 30 rpm, and stood for drying at

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70°C (0.4 kPa - 0.8 kPa) for 15 hours.

[0053] The obtained citalopram hydrobromide crystals weighed 4.2 g, and the crystals had a melting point of 184.4°C and an HPLC purity of 99.9% (254 nm).

5 powder X-ray crystal diffraction pattern: shown in Figure 3
crystal particle size distribution

10 less than 5 µm 17.1%,
not less than 5 µm and less than 10 µm 22.2%,
not less than 10 µm and less than 20 µm 29.1%,
not less than 20 µm and less than 40 µm 27.0%,
not less than 40 µm 4.6% (shown in Figure 6)

15 average particle size 12.9 µm
micrograph (400 magnifications): shown in Figure 13
average aspect ratio: 4.8

Examples 2 - 3

20 [0054] The procedure followed Example 1 except that the cooling time of from 40°C to 20°C and the retention time at 20°C were changed to those shown in Table 1.

Table 1

25 Ex.	Cooling time of from 40°C to 20°C (cooling rate in parenthesis)	Retention time at 20°C	Crystal particle size distribution (D)	Average particle size (µm)
30 2	30 min (40°C/hour)	19 hr 30 min	D<5 µm 31.4% 5 µm≤D<10 µm 30.3% 10 µm≤D<20 µm 25.7% 20 µm≤D<40 µm 12.2% D≥40 µm 0.3% (shown in Figure 7)	7.8
35 3	1 hr (20°C/hour)	19 hr	D<5 µm 19.6% 5 µm≤D<10 µm 26.0% 10 µm≤D<20 µm 31.0% 20 µm≤D<40 µm 21.6% D≥40 µm 1.6% (shown in Figure 8)	11.0
40				
45				
50				

Example 4

55 [0055] Citalopram hydrobromide (5.0 g) was synthesized according to Reference Example 1 and dissolved in methanol (15 ml) at 50°C. Thereto was added active charcoal (0.5 g) and the mixture was stirred for 15 minutes. The active charcoal was filtered off and isopropyl alcohol (25 ml) was added. The mixture was heated to 58°C to dissolve the crystals. When the mixture was cooled to 43°C while stirring at 200 rpm (propeller diameter: 0.05 m), the seed crystal (0.1 mg) of citalopram hydrobromide was added. The mixture was cooled to 41°C over 15 minutes and heated to 50°C

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over 5 minutes, and then stirred at the same temperature for 80 minutes to allow dissolution of a part of the crystals (about half). Then, the mixture was cooled from 50°C to 20°C over 2.5 hours to make the cooling rate almost the same (average cooling rate: 12°C/hour). The cooled suspension was stirred at 20°C for 17.5 hours at 200 rpm and the precipitated crystals were filtrated. The crystals were dried at 50°C (0.67 kPa - 1.33 kPa) for 3 hours in vacuo with stirring at 30 rpm, and stood for drying at 70°C (0.4 kPa - 0.8 kPa) for 15 hours.

[0056] The obtained citalopram hydrobromide crystals weighed 4.1 g and the crystals had an HPLC purity of 99.9% (254 nm) and a melting point of 184.7°C.

powder X-ray crystal diffraction pattern: shown in Figure 4.
crystal particle size distribution

less than 5 µm 9.6%,
not less than 5 µm and less than 10 µm 12.3%,
not less than 10 µm and less than 20 µm 20.9%,
not less than 20 µm and less than 40 µm 31.7%,
not less than 40 µm 25.5% (shown in Figure 9)

average particle size 23.8 µm
micrograph (400 magnifications): shown in Figure 14
average aspect ratio: 5.4

Example 5

[0057] The procedure followed Example 4 except that the cooling time of from 50°C to 20°C and the retention time at 20°C were changed to those shown in Table 2.

Table 2

Ex.	Cooling time of from 50°C to (cooling rate in parenthesis)	Retention time at 20°C	Crystal particle size distribution (D)	Average particle size (µm)
5	30 min (60°C/hr)	19 hr 30 min	D<5 µm 15.6% 5 µm≤D<10 µm 19.3% 10 µm≤D<20 µm 26.9% 20 µm≤D<40 µm 31.0% D≥40 µm 7.2% (shown in Figure 10)	15.1

Example 6

[0058] Citalopram hydrobromide (18.2 kg) was synthesized according to Reference Example 1 and dissolved in methanol (37.4 kg) at 45°C - 50°C. Thereto was added active charcoal (1.8 kg) and the mixture was stirred for 55 minutes. The active charcoal was filtered off and washed with warm methanol (7.2 kg). The washings and the filtrate were combined and heated to about 60°C. Isopropyl alcohol (71.9 kg) heated to 40°C - 50°C was added, and upon confirmation of dissolution at 62°C, the mixture was cooled with stirring at 169 rpm (diameter of impeller of agitator (Pfaudler type): 0.45 m, speed at the tip of impeller of agitator: ca. 4.0 m/s). When the mixture was cooled to 44°C, the seed crystal (about 400 mg) of citalopram hydrobromide was added. Stirring at 40°C - 43°C for 30 minutes enabled confirmation of the precipitation of the crystals at 41.5°C.

[0059] The mixture was cooled from 40°C to 20°C over 4 hours (average cooling rate: 5°C/hour), and further cooled to 10°C over 3 hours. The suspension was stirred at 5°C - 10°C at 80 rpm for 13 hours and the crystals were filtrated. A mixture of isopropyl alcohol (9.6 kg) and methanol (4.8 kg) was cooled to 0°C - 10°C. The crystals were washed with this mixture. The wet crystals (19.8 kg) were dried under reduced pressure (10 kPa - 1.33 kPa), at 30°C - 50°C for 10 hours, at 45°C - 55°C for 5 hours, and at 70°C - 75°C for 8 hours, with stirring at 30 rpm.

[0060] The obtained citalopram hydrobromide crystals weighed 15.0 kg (recrystallization yield : 82%) and the crystals had an HPLC purity of 99.75% (220 nm) and a melting point of 185.0°C.

crystal particle size distribution

less than 5 μm 12.6%,
not less than 5 μm and less than 10 μm 20.2%,
not less than 10 μm and less than 20 μm 35.5%,
not less than 20 μm and less than 40 μm 29.3%,
not less than 40 μm 2.4% (shown in Figure 11)

average particle size: 14.6 μm
micrograph (400 magnifications): shown in Figure 15.
average aspect ratio: 3.0
bulk density: 0.2 g/ml
tap density 0.42 g/ml

Comparative Example 1

[0061] Citalopram hydrobromide (5.0 g) was synthesized according to Reference Example 1 and dissolved in methanol (15 ml) at 50°C. Thereto was added active charcoal (0.5 g) and the mixture was stirred for 15 minutes. The active charcoal was filtered off and isopropyl alcohol (25 ml) was added. The mixture was heated to 58°C to dissolve the crystals. The mixture was cooled to 40°C over 5 min and then cooled from 40°C to 20°C over 5 min with stirring at 200 rpm. When the mixture was cooled to 20°C, the seed crystal (0.1 mg) was added. The mixture was stirred at the same temperature for 20 hours and the crystals were filtrated. The crystals were dried at 50°C (0.67 kPa - 1.33 kPa) for 3 hours in vacuo with stirring at 30 rpm, and stood for drying at 70°C (0.4 kPa - 0.8 kPa) for 15 hours.

[0062] The obtained citalopram hydrobromide crystals weighed 4.3 g and the crystals had an HPLC purity of 99.9% (254 nm) and a melting point of 184.2°C.

powder X-ray crystal diffraction pattern: shown in Figure 5
crystal particle size distribution

less than 5 μm 41.9%,
not less than 5 μm and less than 10 μm 30.2%,
not less than 10 μm and less than 20 μm 23.9%,
not less than 20 μm and less than 40 μm 4.0%,
not less than 40 μm 0% (shown in Figure 12)

average particle size: 6.3 μm
micrograph (400 magnifications): shown in Figure 16

[0063] According to the method of the present invention, the crystal characteristics of citalopram hydrobromide, such as particle size, particle size distribution, aspect ratio and the like, can be controlled easily and industrially. In addition, citalopram hydrobromide crystals having crystal characteristics useful as a pharmaceutical bulk can be provided.

Claims

1. Citalopram hydrobromide crystals containing crystals having a particle size of less than 5 μm in a proportion of 35% at most.
2. The citalopram hydrobromide crystals of claim 1, which comprise crystals having a particle size of not less than 20 μm in a proportion of not less than 10%.
3. The citalopram hydrobromide crystals of claim 1, which have an average aspect ratio of not less than 2.0 and not more than 9.0.
4. The citalopram hydrobromide crystals of claim 1, which have an average aspect ratio of not less than 2.5 and less than 4.5.
5. The citalopram hydrobromide crystals of claim 1, which have an average aspect ratio of not less than 4.5 and not

more than 6.0.

6. Citalopram hydrobromide crystals having an average aspect ratio of not less than 2.0 and not more than 9.0.

5 7. Citalopram hydrobromide crystals having an average aspect ratio of not less than 2.5 and less than 4.5.

8. Citalopram hydrobromide crystals having an average aspect ratio of not less than 4.5 and not more than 6.0.

9. A method for crystallizing citalopram hydrobromide, which comprises the steps of

10

(A1) dissolving, by heating, citalopram hydrobromide in a solvent comprising at least one member selected from the group consisting of alcohol having 1 to 3 carbon atoms, water and acetone and
(B1) cooling the resulting product to allow for crystallization while controlling a cooling rate.

15 10. The method of claim 9, which comprises controlling the cooling rate of the solution in a temperature range of from 0°C to 80°C.

11. The method of claim 9, which comprises controlling an average cooling rate of the solution in the temperature range of from 20°C to 40°C to not less than 30°C/hour and not more than 60°C/hour.

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12. The method of claim 9, which comprises controlling an average cooling rate of the solution in a temperature range of from 20°C to 40°C to not less than 0.5°C/hour and less than 30°C/hour.

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13. The method of claim 9, which comprises, after cooling to a temperature range of from not less than 30°C to less than 48°C, adding a seed crystal of citalopram hydrobromide for crystallization.

14. A method for crystallizing citalopram hydrobromide, which comprises the steps of

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(A2) dissolving, by heating, citalopram hydrobromide in a solvent comprising at least one member selected from the group consisting of alcohol having 1 to 3 carbon atoms, water and acetone,
(B2) cooling the obtained solution to achieve crystallization,
(C2) dissolving a part of the obtained crystals by heating, and
(D2) recrystallizing while controlling a cooling rate.

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15. The method according to claim 14, which comprises cooling to a temperature range of from not less than 30°C to less than 48°C in (B2).

16. The method according to claim 14, which comprises, after cooling to a temperature range of from not less than 30°C to less than 48°C, adding a seed crystal of citalopram hydrobromide for crystallization in (B2).

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17. The method according to claim 14, which comprises dissolving a part of the crystals by heating to not less than 48°C and not more than 60°C in (C2).

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18. The method according to claim 14, which comprises controlling the average cooling rate of the solution in the temperature range of from (heating temperature in (C2)) to (said heating temperature - 30°C) to not less than 30°C/hour and not more than 90°C/hour in (D2).

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19. The method according to claim 14, which comprises controlling the average cooling rate of the solution in the temperature range of from (heating temperature in (C2)) to (said heating temperature - 30°C) to not less than 1°C/hour and less than 30°C/hour in (D2).

55

Fig.1

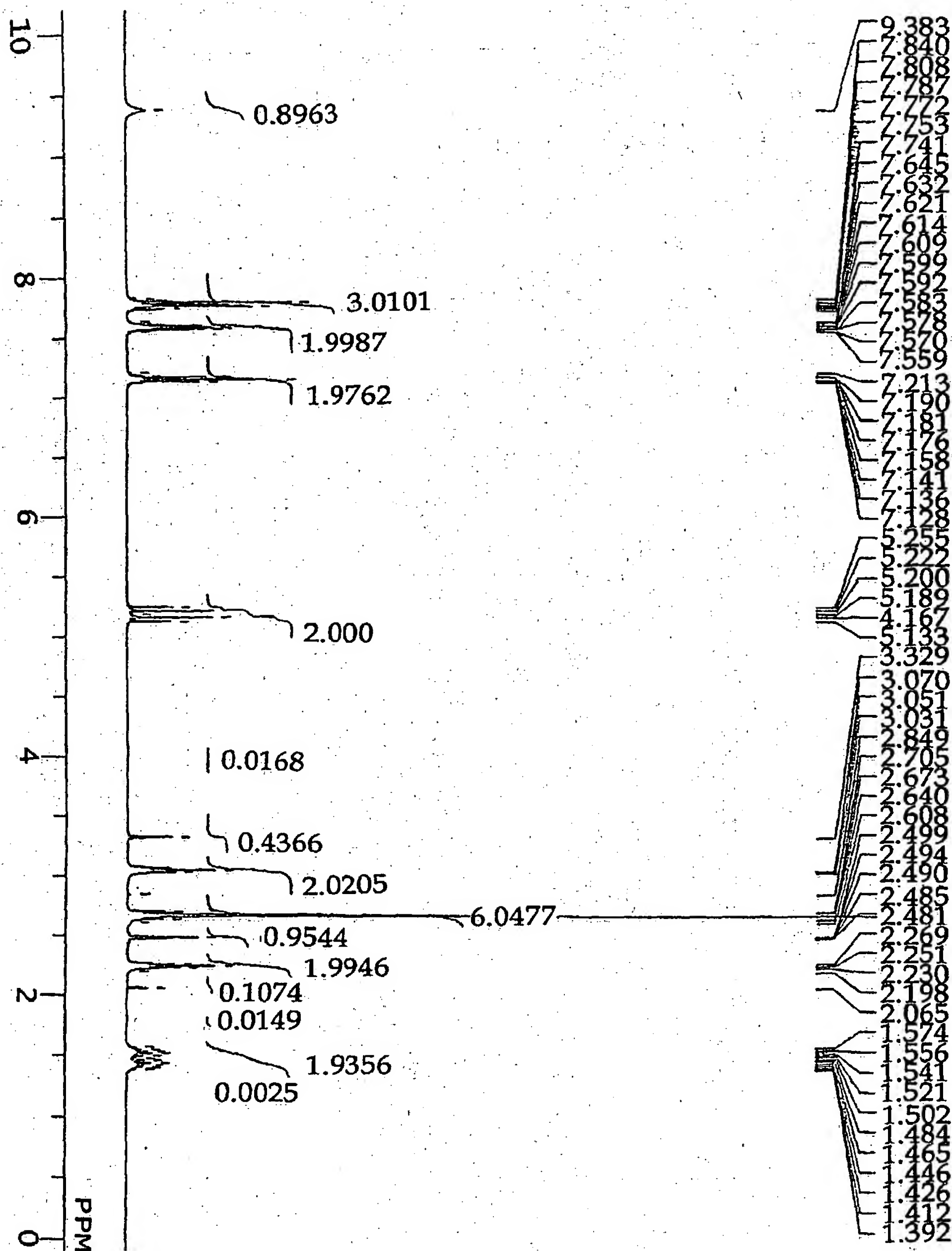


Fig.2

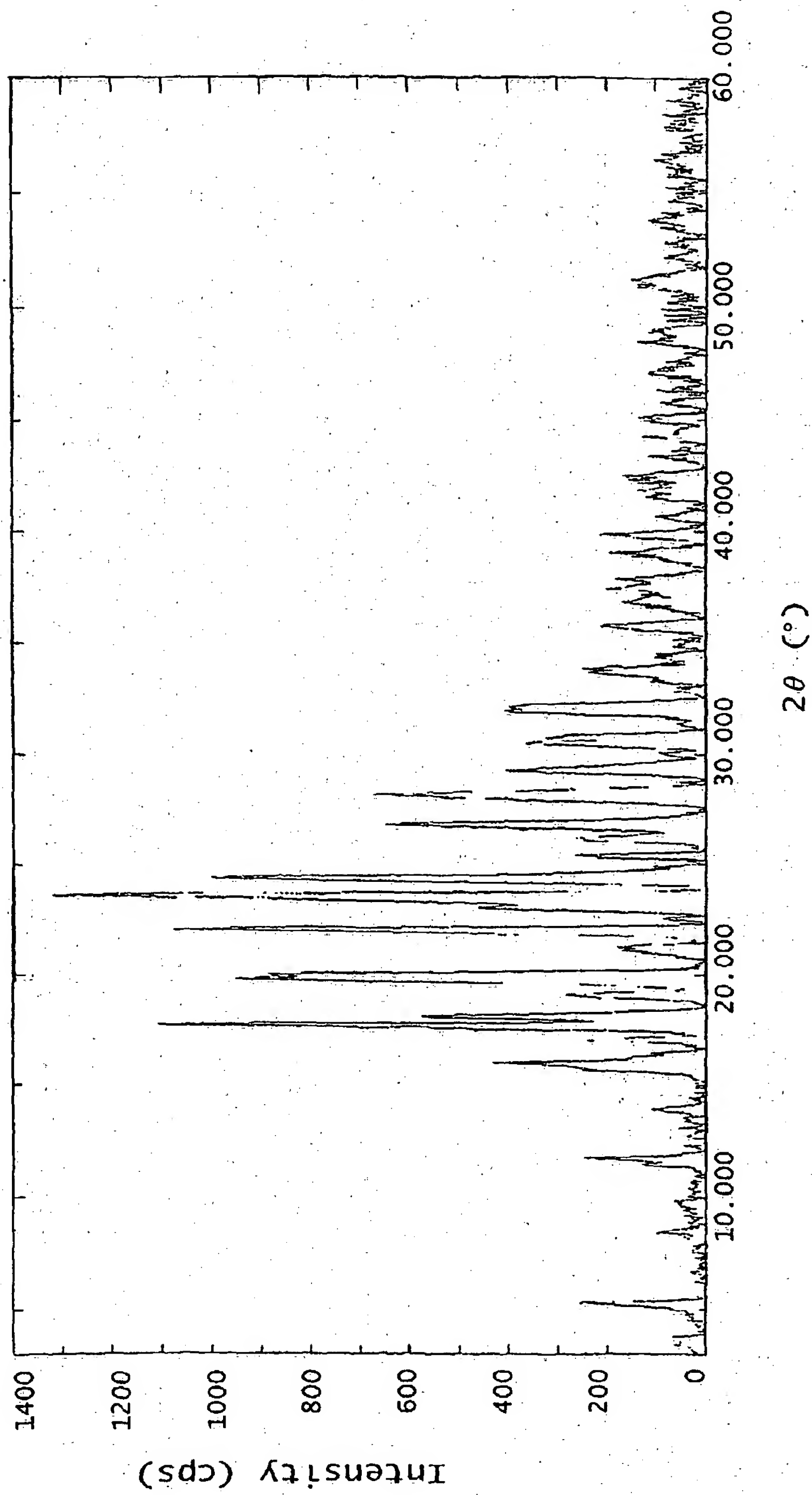


Fig.3

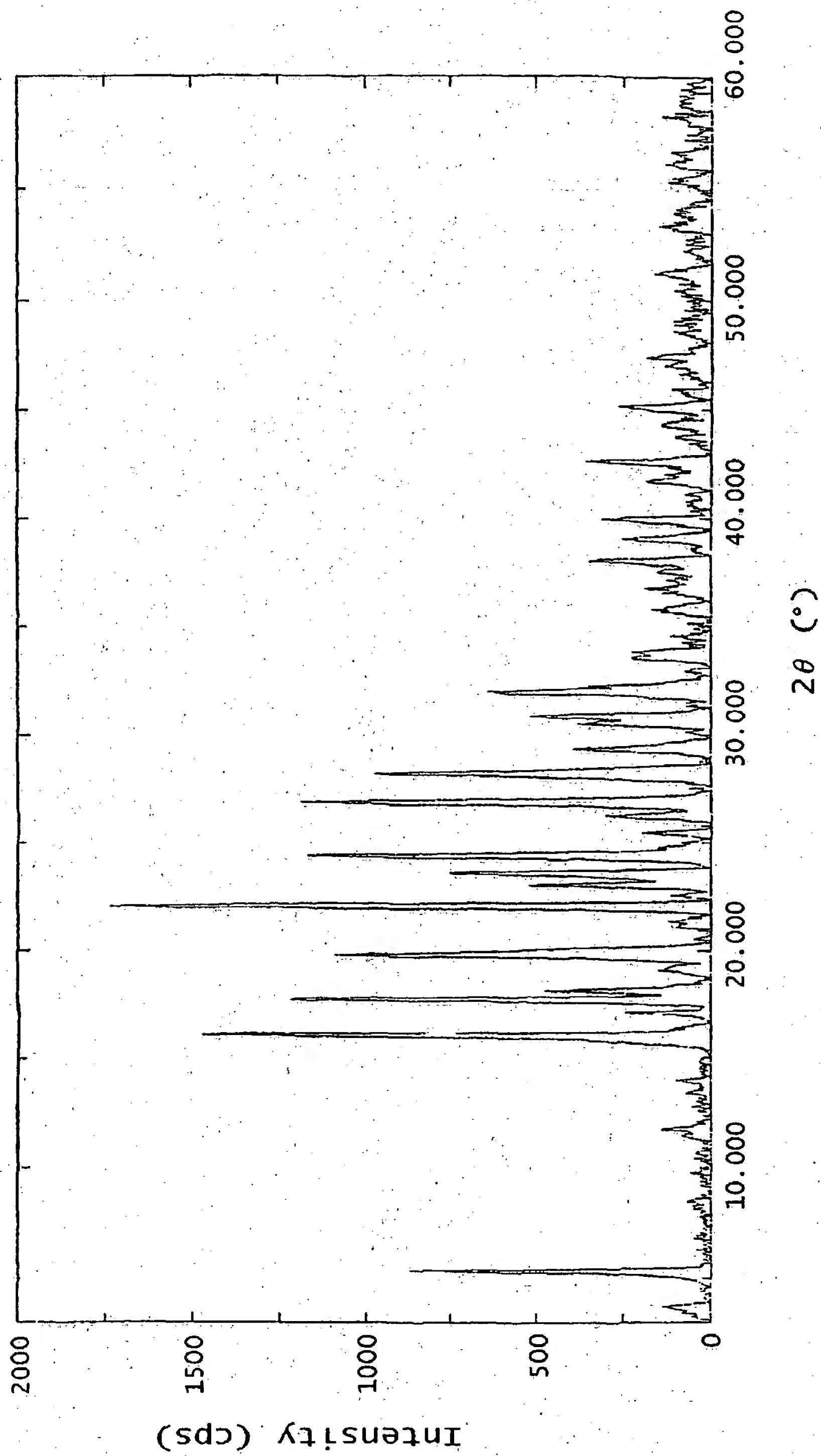


Fig.4

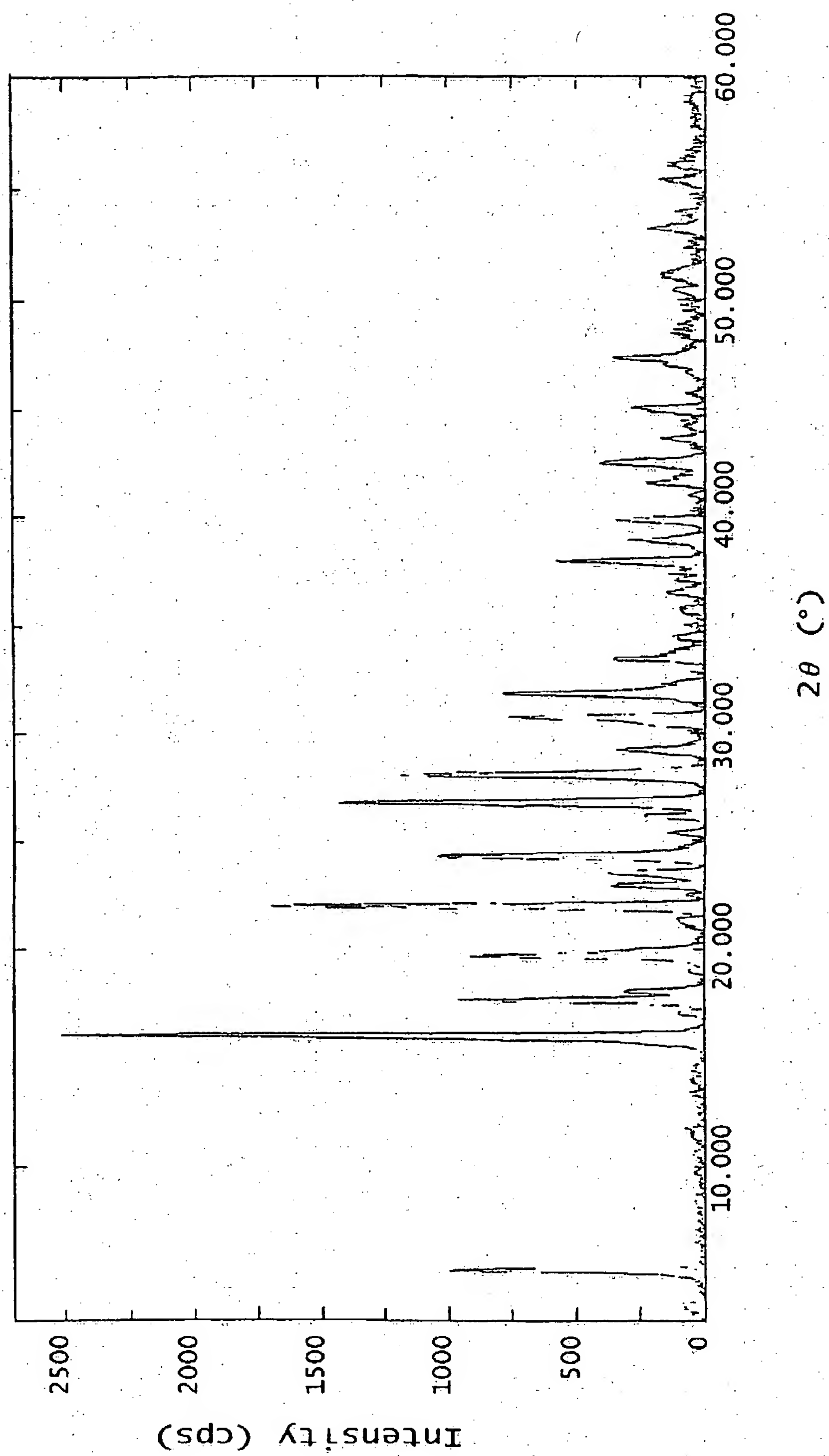


Fig.5

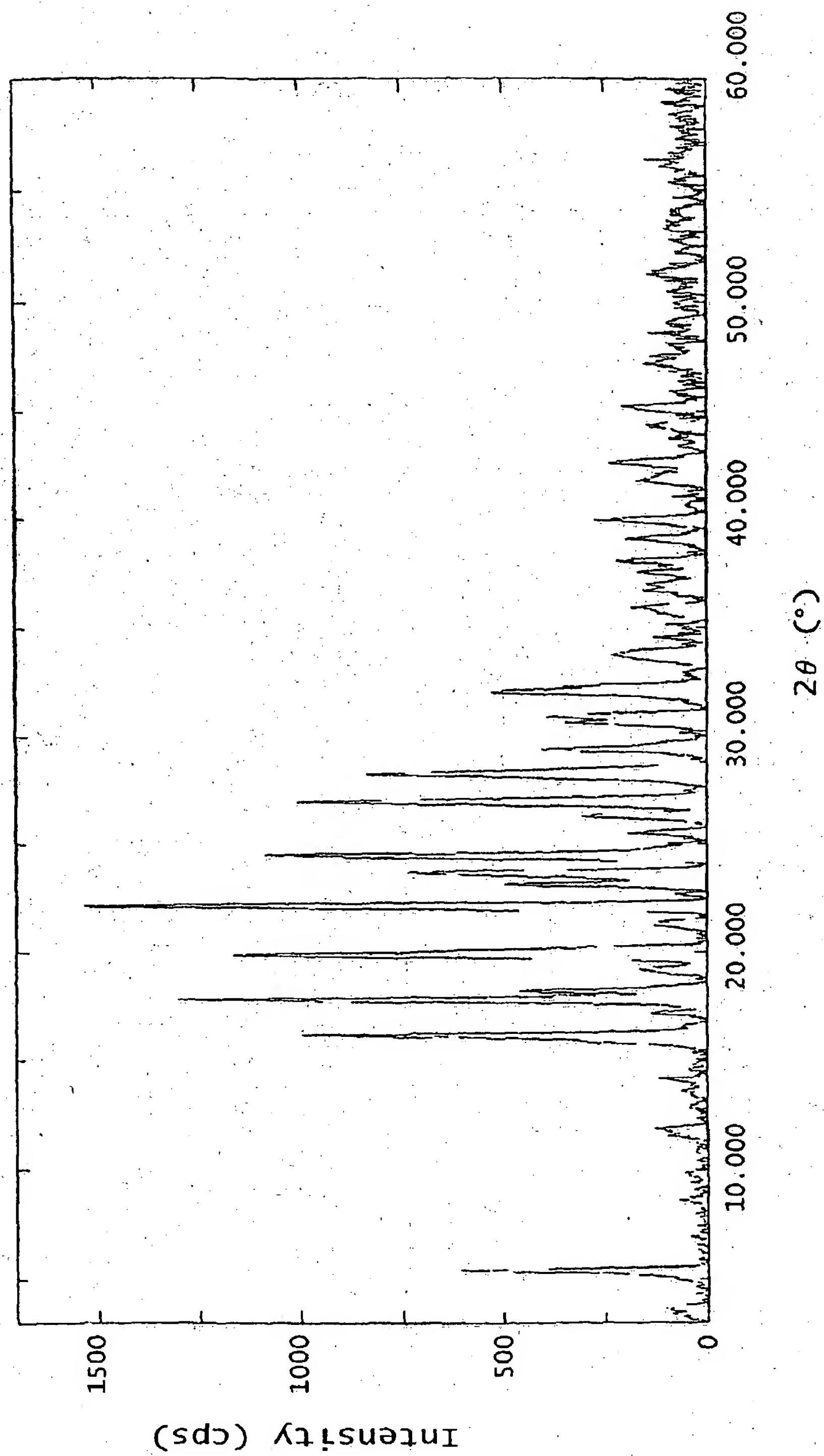


Fig.6

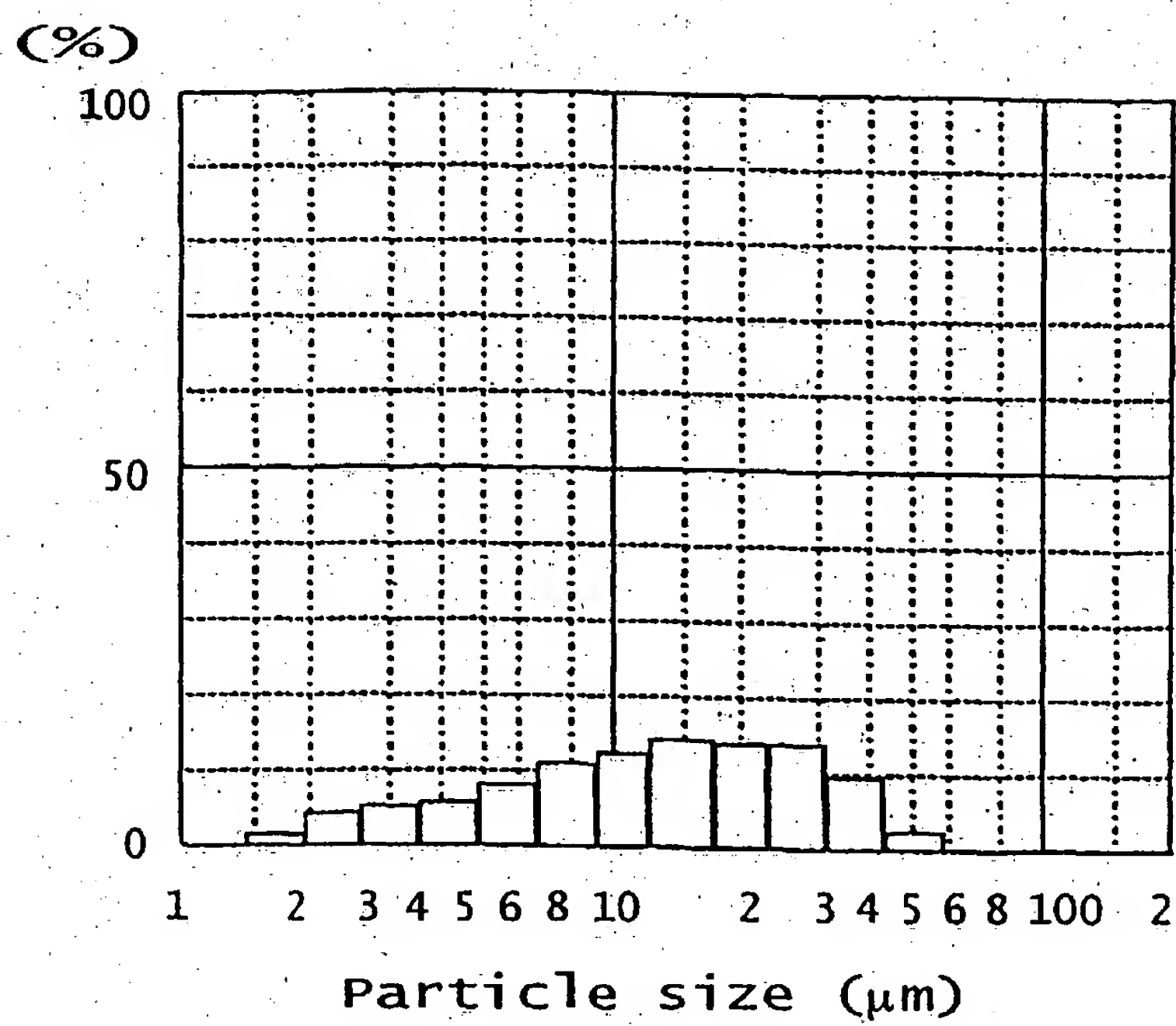


Fig.7

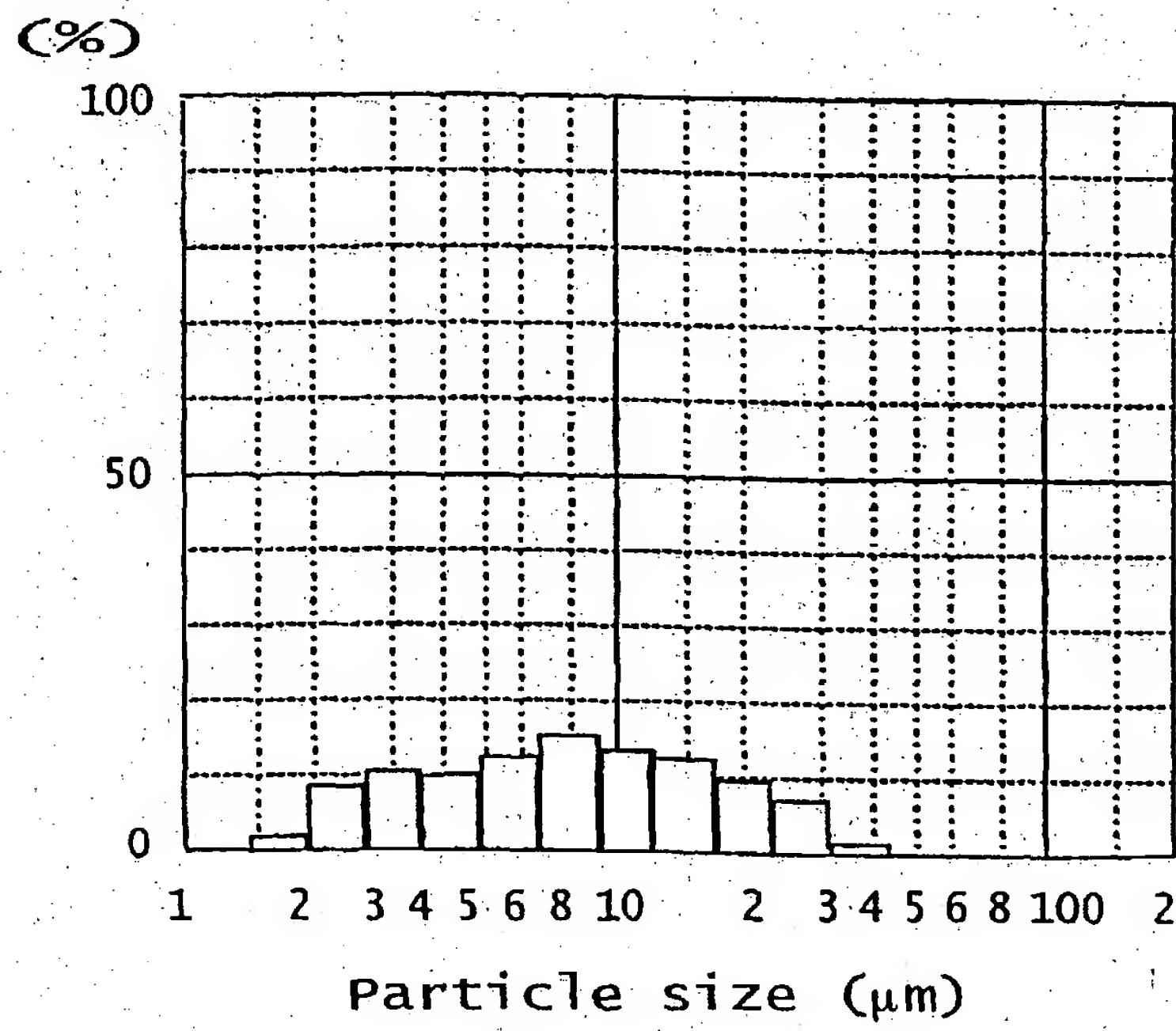


Fig.8

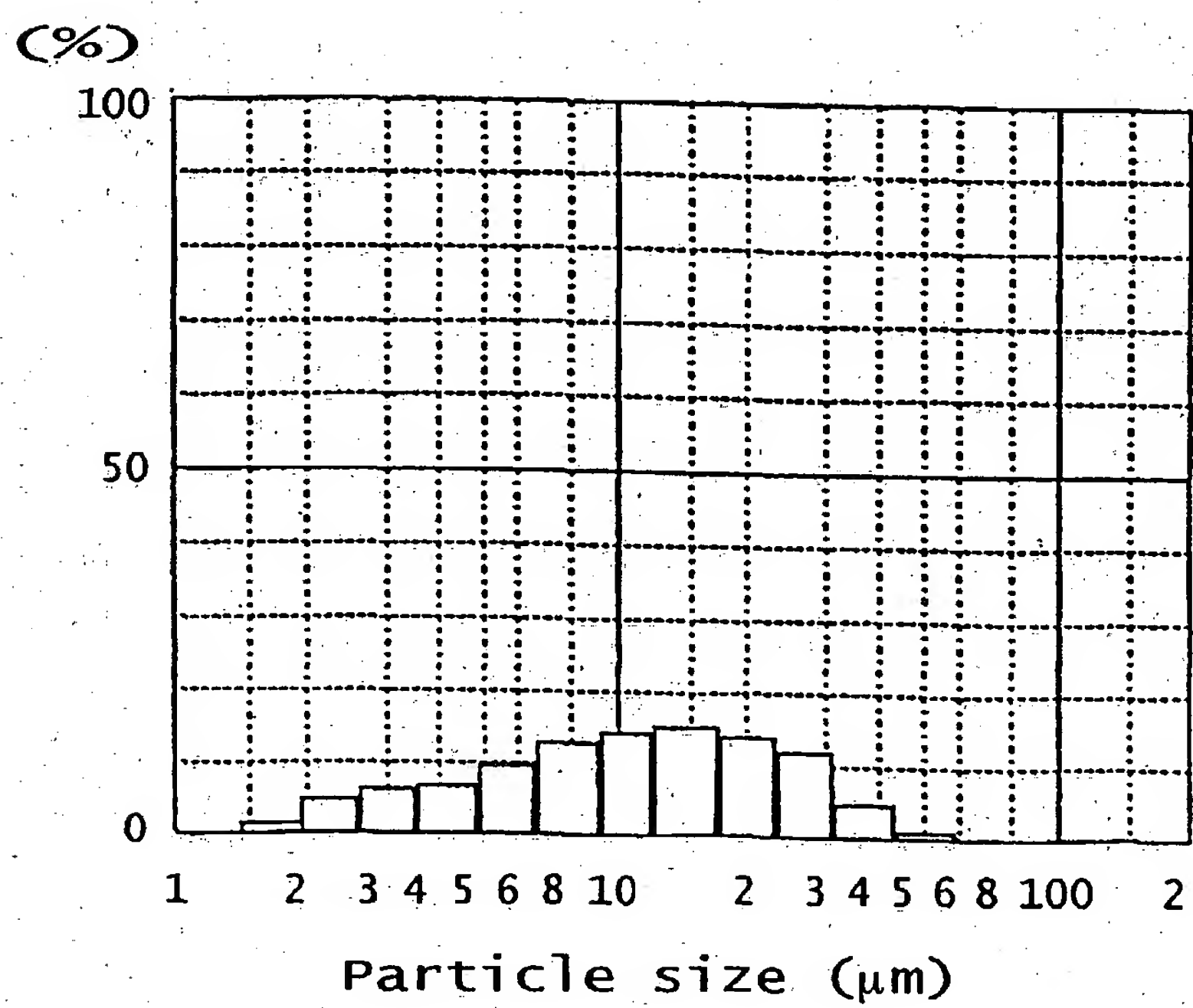


Fig.9

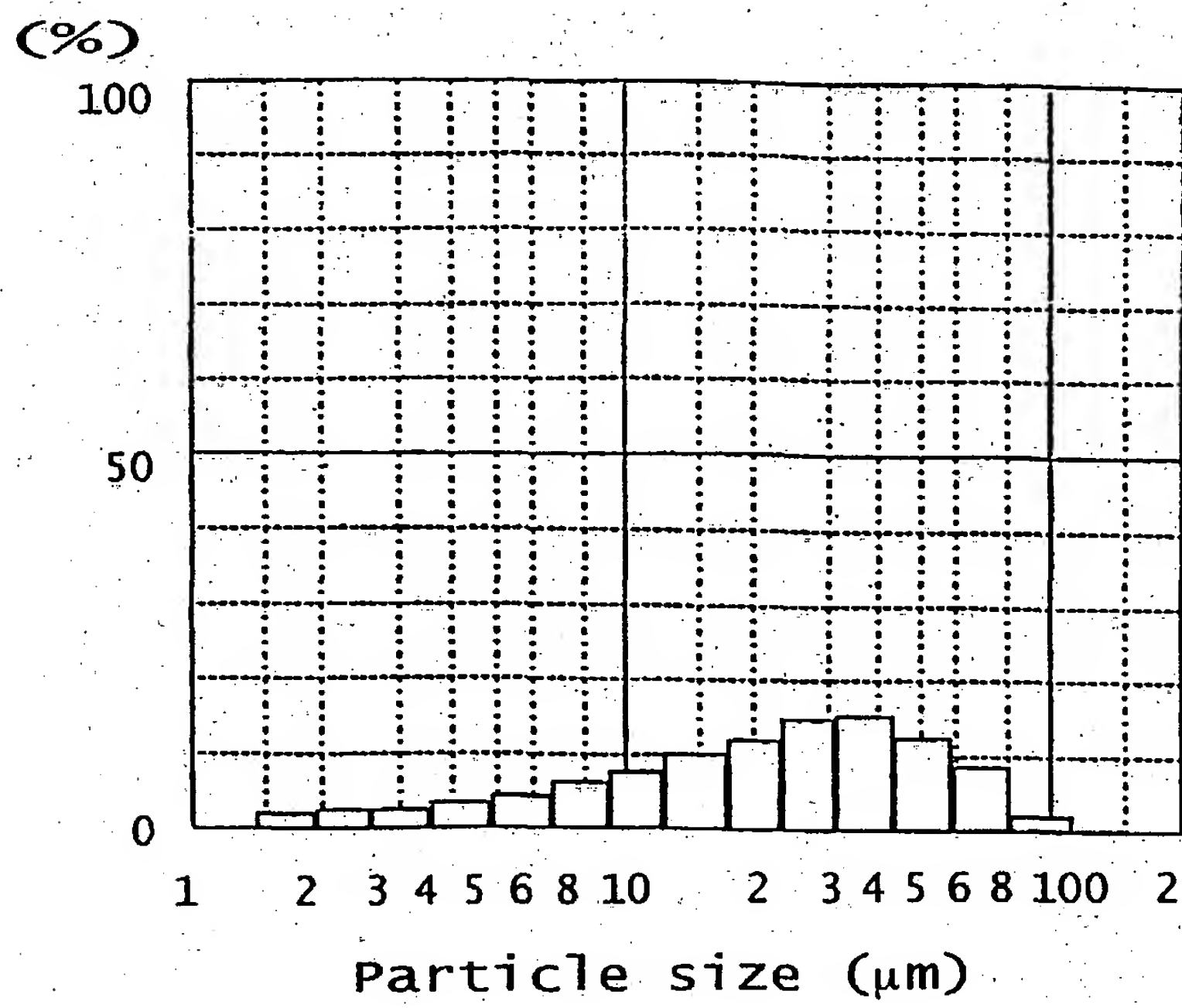


Fig.10

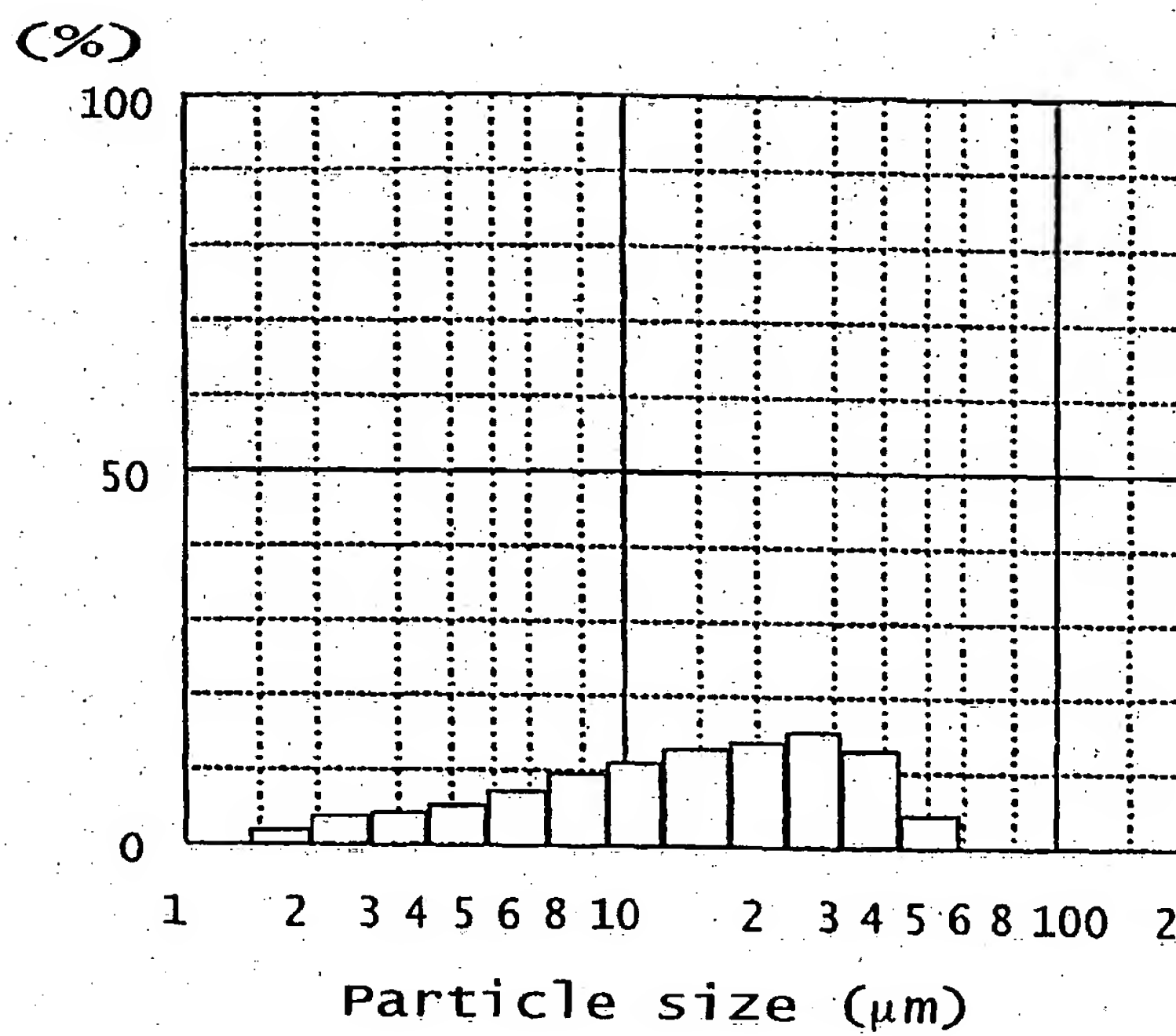


Fig.11

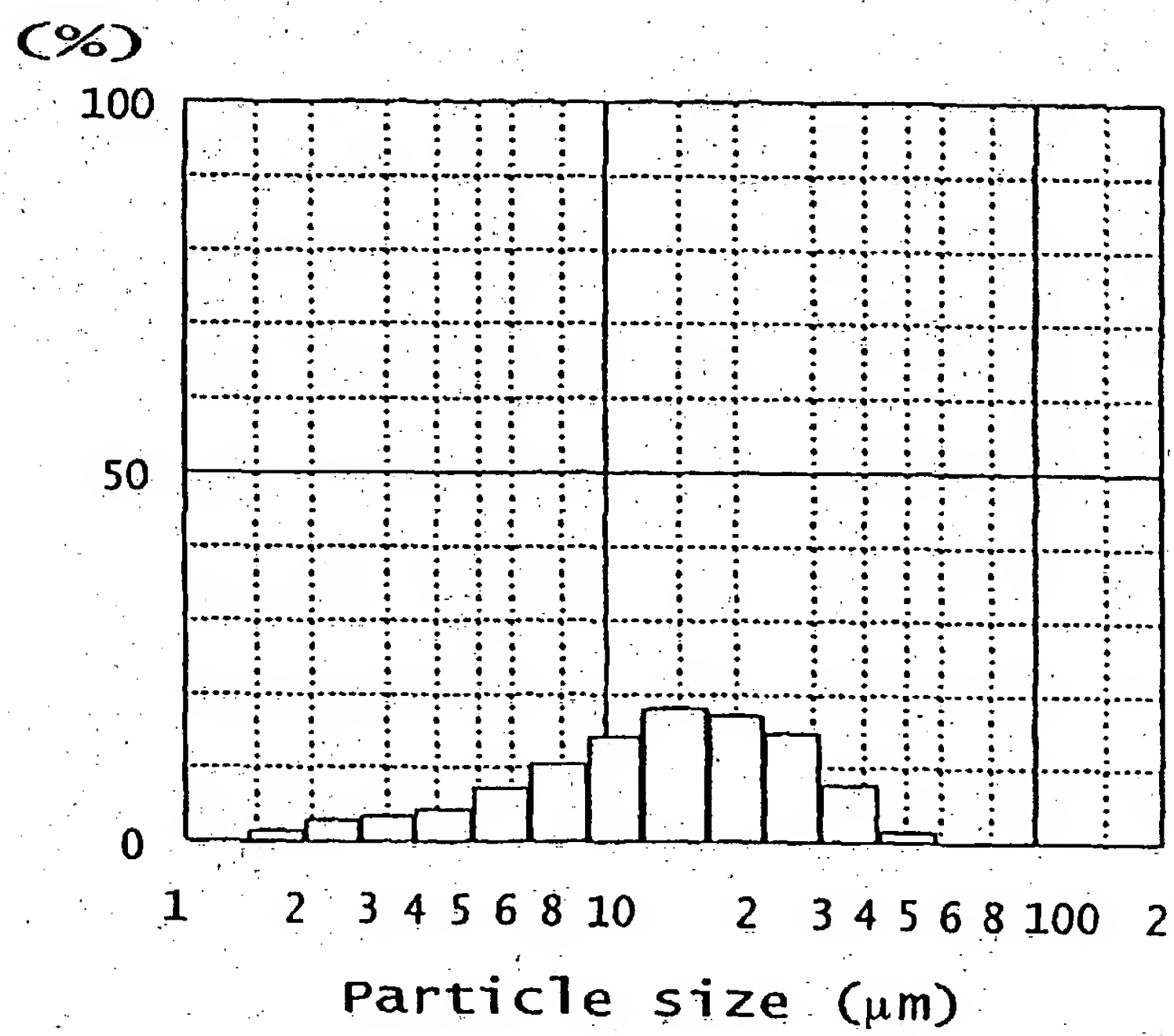


Fig.12

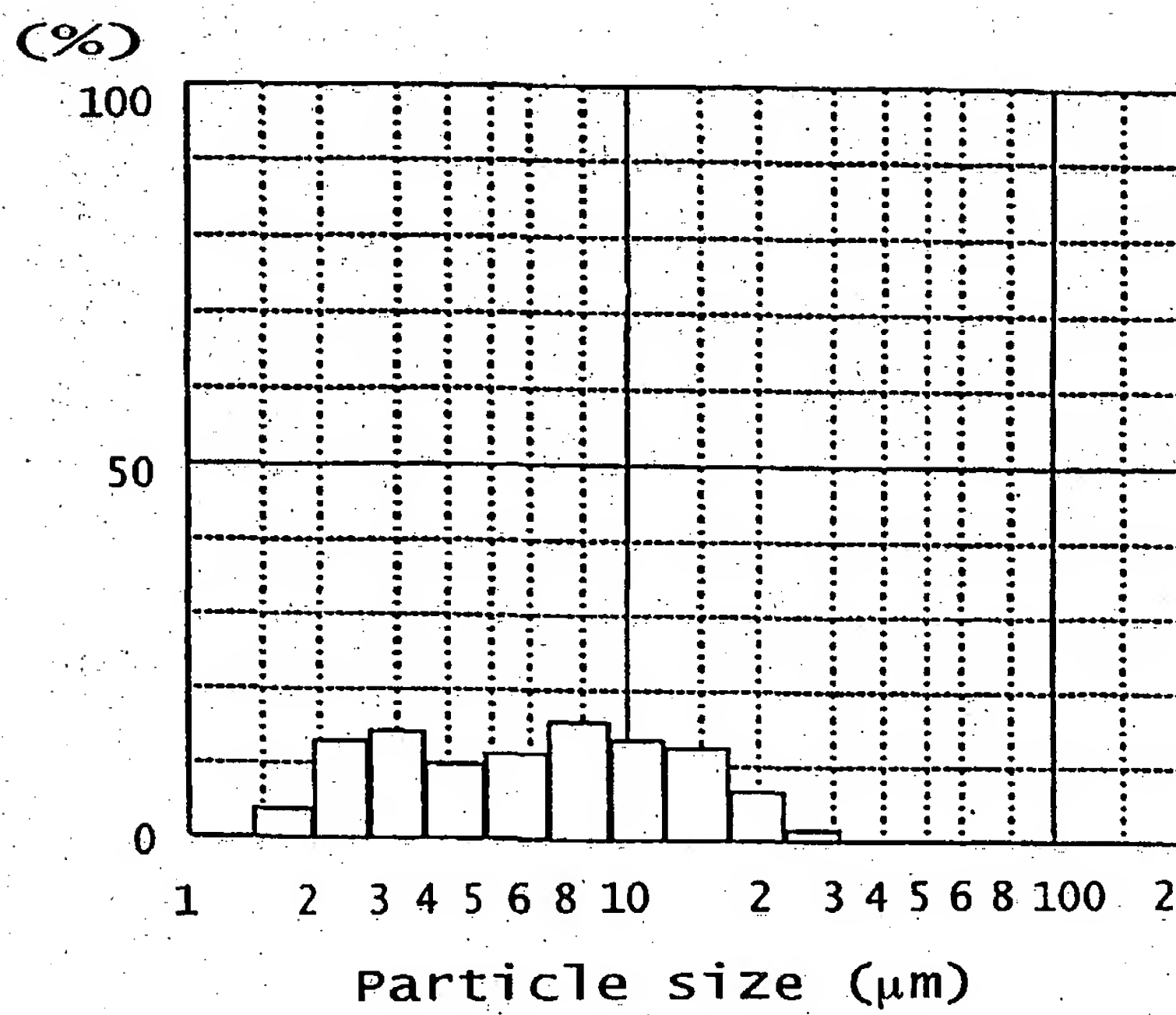


Fig.13

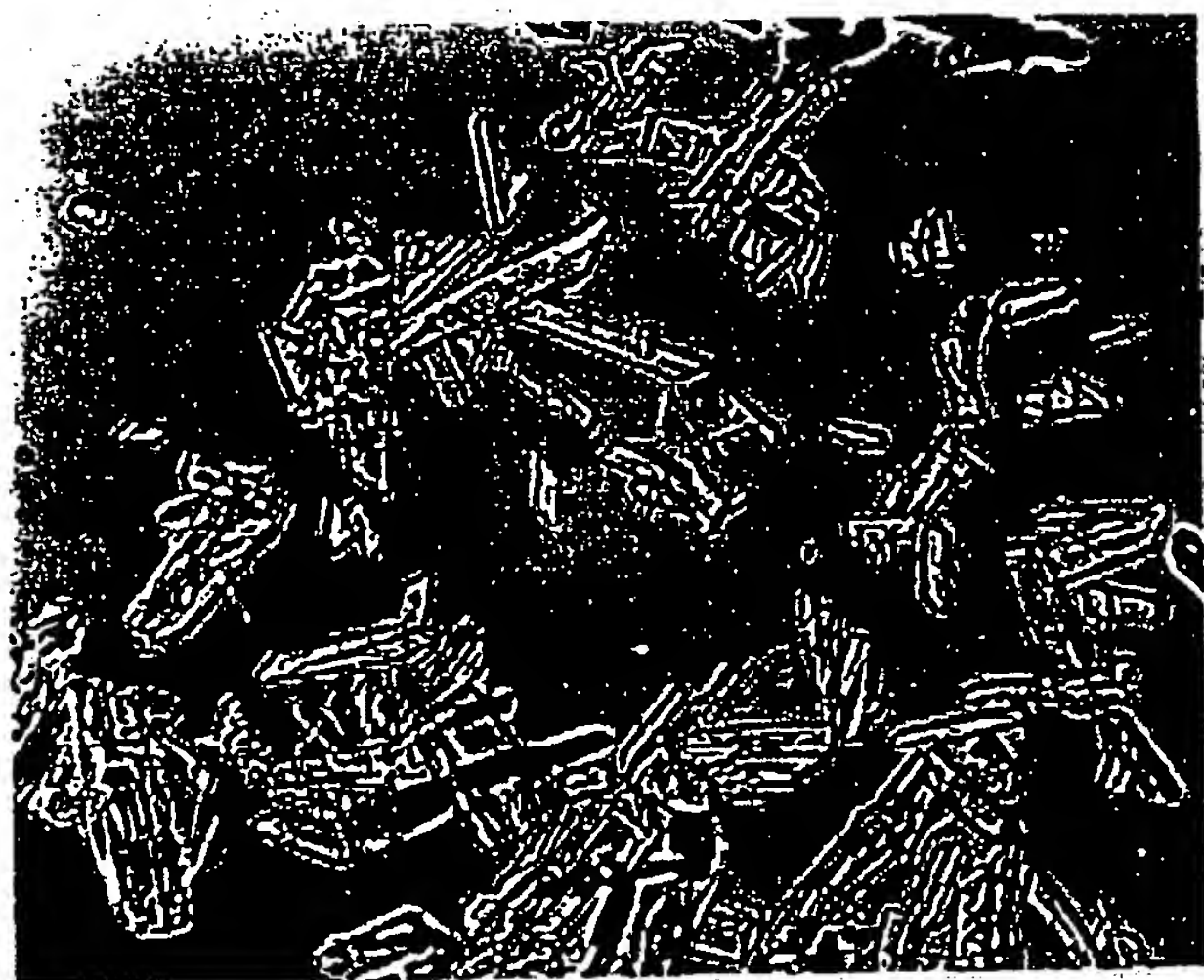


Fig.14

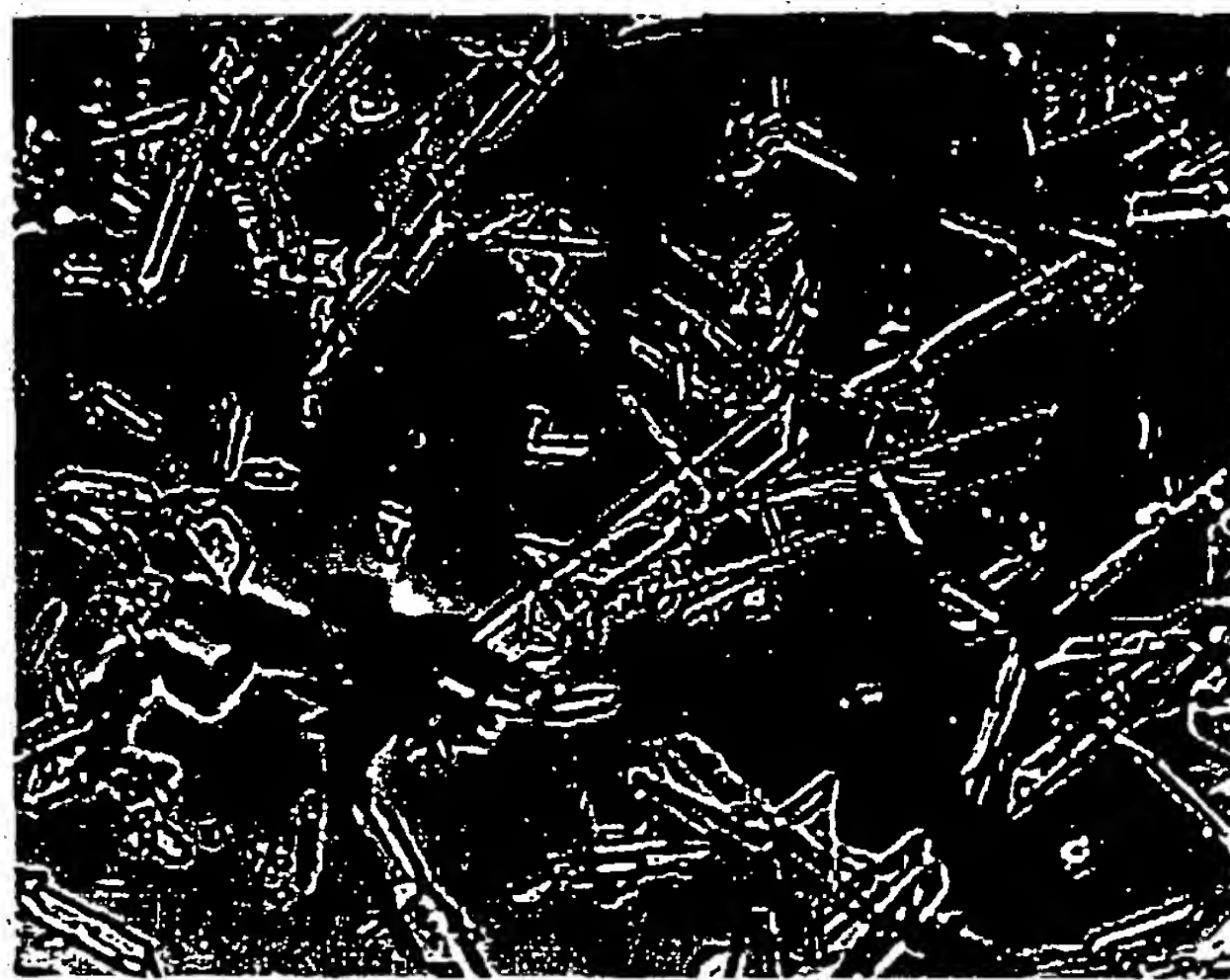


Fig.15



Fig.16

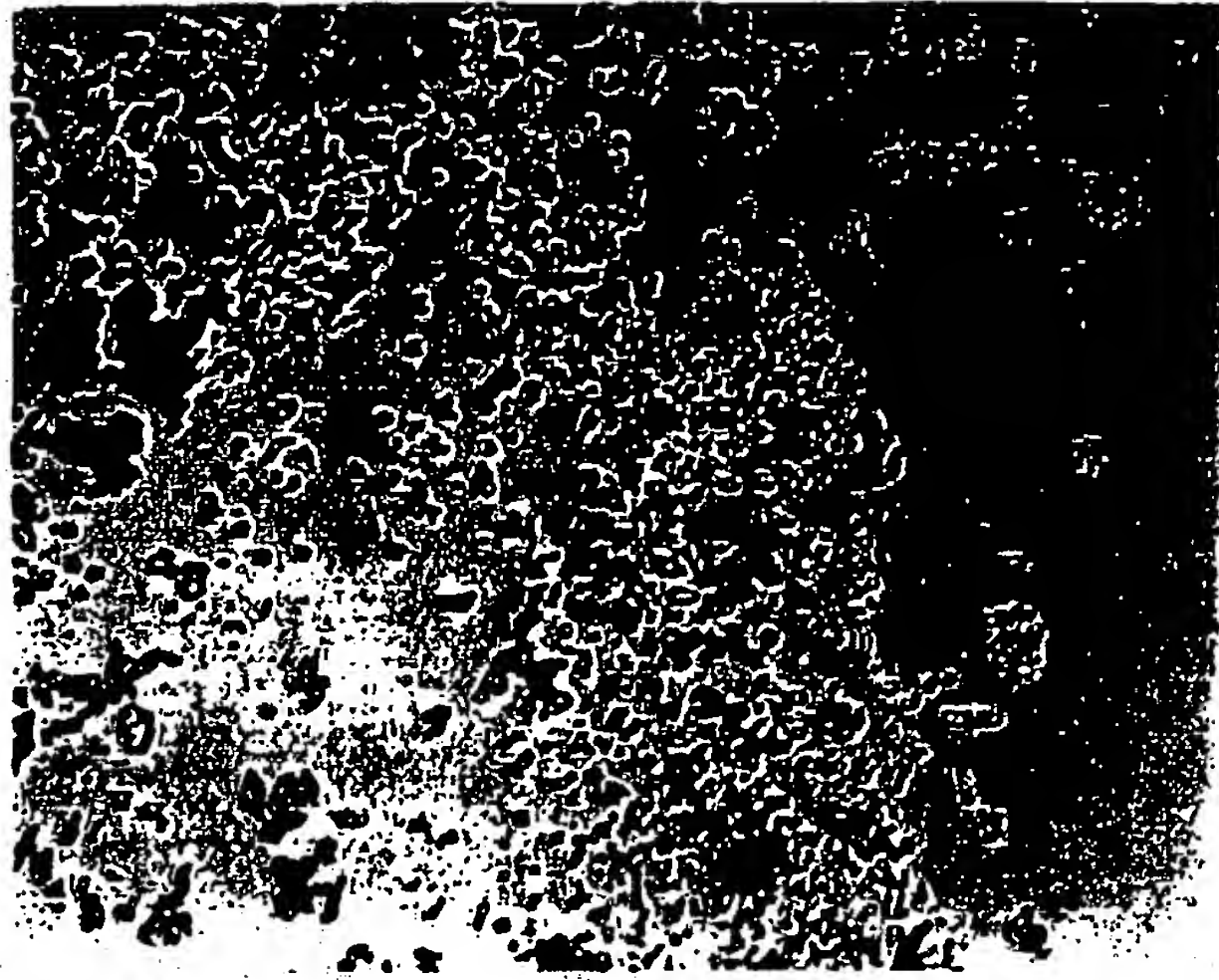
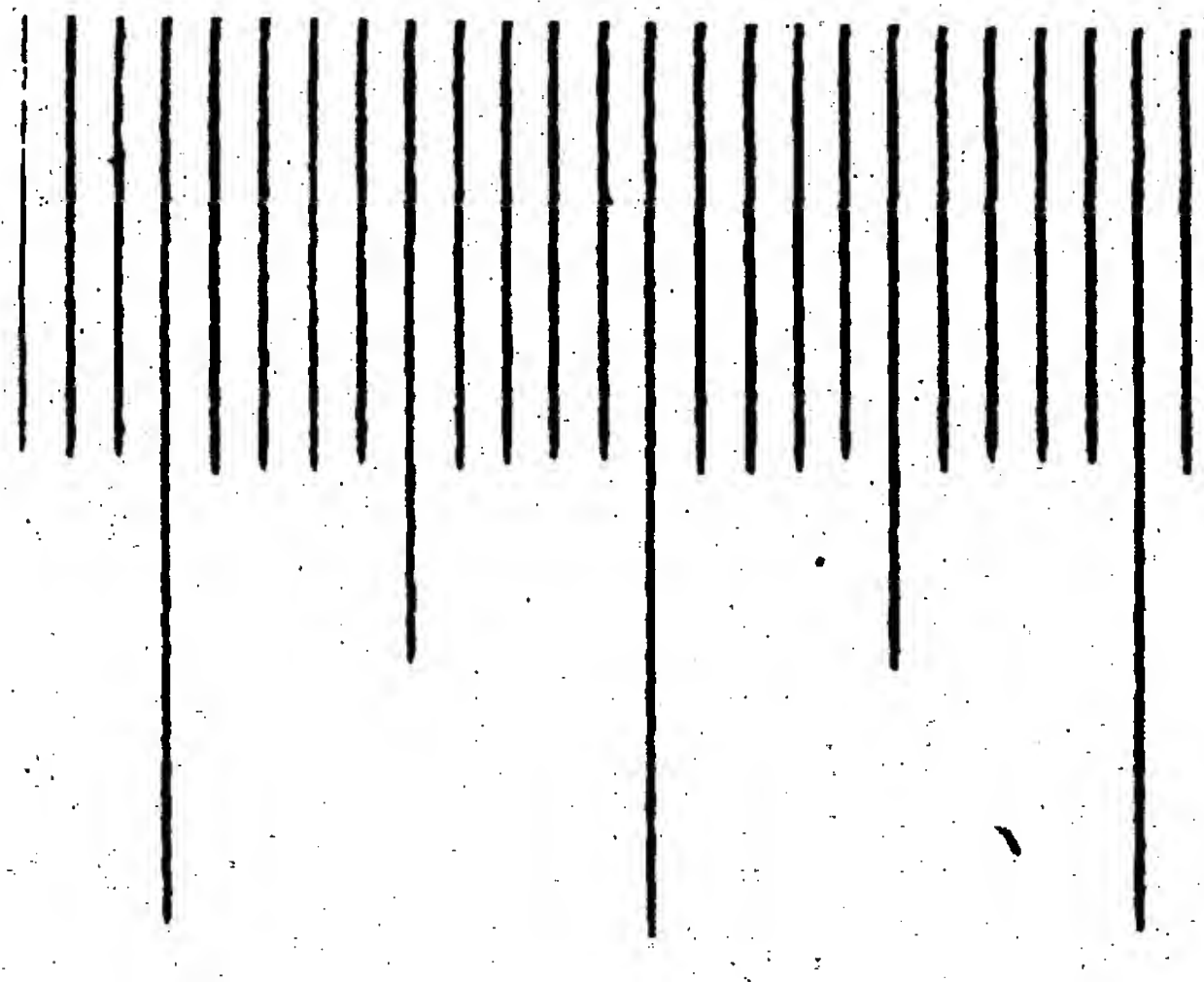


Fig.17





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EUROPEAN SEARCH REPORT

Application Number

EP 01 10 8914

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	WO 00 23431 A (H. LUNDBECK A/S) 27 April 2000 (2000-04-27)	1-10, 14	C07D307/87
Y	* page 15, line 18 - line 25 *	11-13, 15-19	
X,P	DE 200 07 303 U (H. LUNDBECK A/S) 27 July 2000 (2000-07-27) * the whole document *	1-8	
X,D	US 4 650 884 A (KLAUS P. BOGESO) 17 March 1987 (1987-03-17)	1-10, 14	
Y	* the whole document *	11-13, 15-19	
A	US 4 136 193 A (KLAUS P. BOGESO) 23 January 1979 (1979-01-23) * the whole document *	1-19	
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			C07D
Place of search		Date of completion of the search	Examiner
MUNICH		19 July 2001	Kyriakakou, G
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**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 01 10 8914

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19-07-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0023431 A	27-04-2000	AU 6326099 A	08-05-2000
DE 20007303 U	27-07-2000	AT 4364 U	25-06-2001
		GB 2357762 A	04-07-2001
		NL 1016435 C	06-11-2000
US 4650884 A	17-03-1987	AT 38661 T	15-12-1988
		AU 574819 B	14-07-1988
		AU 4577685 A	13-02-1986
		CA 1237147 A	24-05-1988
		DE 3566251 D	22-12-1988
		DK 89595 A	10-08-1995
		DK 356285 A	07-02-1986
		EP 0171943 A	19-02-1986
		ES 545885 D	01-04-1986
		ES 8606257 A	01-10-1986
		FI 852902 A, B,	07-02-1986
		GR 851894 A	03-12-1985
		IE 57817 B	21-04-1993
		IL 75690 A	31-10-1988
		JP 1902596 C	08-02-1995
		JP 6025099 B	06-04-1994
		JP 61087654 A	06-05-1986
		NO 853091 A, B,	07-02-1986
		NZ 212541 A	30-05-1988
		PT 80913 A, B	01-09-1985
		ZA 8505026 A	25-06-1986
US 4136193 A	23-01-1979	GB 1526331 A	27-09-1978
		AT 360001 B	10-12-1980
		AT 571979 A	15-05-1980
		AT 360002 B	10-12-1980
		AT 572079 A	15-05-1980
		AT 359488 B	10-11-1980
		AT 947276 A	15-04-1980
		AU 509445 B	15-05-1980
		AU 2107377 A	13-07-1978
		BE 850401 A	14-07-1977
		CA 1094087 A	20-01-1981
		CH 626886 A	15-12-1981
		CH 632258 A	30-09-1982
		CH 632259 A	30-09-1982
		DE 2657013 A	28-07-1977
		DK 13177 A, B,	15-07-1977
		ES 454980 A	01-04-1978
		FI 770073 A, B,	15-07-1977

EPC FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 01 10 8914

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19-07-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4136193 A		FR 2338271 A	12-08-1977
		IE 44055 B	29-07-1981
		JP 1368581 C	11-03-1987
		JP 52105162 A	03-09-1977
		JP 61035986 B	15-08-1986
		NL 7700244 A,B,	18-07-1977
		NO 770109 A,B,	15-07-1977
		NZ 183001 A	02-06-1978
		SE 429551 B	12-09-1983
		SE 7614201 A	15-07-1977
		ZA 7700057 A	30-11-1977

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82